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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,794	08/04/2003	Huai-Jen Tsai	8961-000004/US	5554

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,794	TSAI, HUAI-JEN	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/05/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *1 and 2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 06/05/2006 has been received. Claims 3 and 5-9 have been amended. Claims 10-13 have been added.

Claims 1 and 2 were previously withdrawn as being drawn to a non-elected invention. However, after further consideration, it is deemed to not require undue burden to examine claims 1 and 2 along with the other pending claims. Therefore, claims 1 and 2 are hereby rejoined with claims 3-13. Claims 1-13 are pending and under consideration in the instant office action.

Specification

The substitute specification containing numbered pages is noted.

The disclosure is objected to because of the following informalities: The specification contains drawings at page 4, which are not permitted to be part of the specification [see MPEP 608.01 (VI) and 37 CFR 1.58(a)]. The drawings embedded in the specification should be removed from the specification. Reference to the Figures 4 and 5 could be substituted as deemed appropriate.

Appropriate correction is required.

Claim Objections

The previous objections to the claims are withdrawn with the exception of claim 4.

Claim 4 remains objected to and newly considered claim 2 is objected to because of the following informalities: Claims 2 and 4 contain drawings, which are not permitted to be part of the specification, including the claims [see MPEP 608.01 (VI) and 37 CFR 1.58(a)]. Applicant

has argued that the drawing in claim 4 is a chemical formula. This argument is not persuasive. A diagrammatic drawing of a plasmid is not a chemical structure. Appropriate correction is required.

Claim 2 is objected to because of the following informalities: Claim 2 contains the terminology "fluorescence gene", which is awkward. Use of the terminology "gene encoding a fluorescent gene product" is preferable. Appropriate correction is required.

Claim 3 is objected to because of the following informalities: Claim 3 contains 2 steps labeled as step (f). Appropriate correction is required.

Claims 1,10 and 12 are objected to because of the following informalities: The language of claims 1,10 and 12 is awkward. Modifiers such as "a" or "an" or "the" are lacking. For example, line 4 of claim 10 should read, "a gene encoding". Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 remains rejected and newly considered claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments have been fully considered but are not persuasive. The rejection is maintained for reasons of record set forth at pages 4-6 of the previous office action and applied to newly considered claim 2.

A deposit requirement has been made to meet the enablement requirements for claim 4 and is now applied to claim 2 (see pages 4-5 of the previous office action dated 03/03/2006). Applicant argues that the specification provides an enabling disclosure for the claimed construct. In response, claim 4 refers to two single, specific plasmids by name, p-αDsRedITR (8.0 kb) and p-αEGFPITR (8.1 kb). The claim is not generically drawn to any plasmid comprising the claimed elements that would result by carrying what is disclosed in the specification. Any plasmid made by the methods disclosed in the specification would not result in the claimed p-αDsRedITR (8.0 kb) and p-αEGFPITR (8.1 kb) but some other plasmid with similar or nearly identical properties.

The additional aspects of the rejection concerning observing fluorescence in the eggs is withdrawn in light of Applicant's amendment to the claims, however, the amendment necessitates a rejection under 35 USC 112, 2nd paragraph as set forth below.

The rejection of claims 3 and 5-9 under 35 U.S.C. 112, first paragraph, is withdrawn in light of Applicant's amendments to the claims. However, similar grounds of rejection are necessary for newly considered claim 1 as set forth below.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene fragment comprising a zebrafish α-actin gene promoter operably linked to a gene encoding a fluorescent protein wherein the promoter and gene are flanked by

adeno-associated virus inverted terminal repeats, does not reasonably provide enablement for the claimed construct wherein the promoter and fluorescence-encoding gene are not operably linked. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claim is drawn to a gene fragment comprising an α -actin gene promoter and a fluorescence-encoding gene. The claims fail to require operable linkage of the promoter to the fluorescence-encoding gene. Placement of a promoter in a plasmid construct or other gene

fragment with a gene encoding a fluorescent product will not necessarily lead to expression of the gene. One would not know how to use the claimed gene fragment or plasmid without operable linkage. The claims should require operable linkage of the promoter to the gene. The specification teaches a use for the claimed fragment or plasmid wherein the α-actin promoter drives expression of a fluorescent reporter gene but does not teach how to use the claimed fragment or plasmid fails to lead to gene expression. Thus, the specification does not teach how to use the claimed fragment or plasmid wherein the promoter and the fluorescence gene are not operably linked.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear by use of the terminology "promoter of golden zebrafish". It is unclear if it is referring to a promoter designed for use in golden zebrafish, is a promoter that works only in golden zebrafish or is a promoter isolated from golden zebrafish. Claim 2 depends from claim 1.

Claim 3 is unclear because it refers to eggs that have been incubated for 24 hours as "eggs". It is unclear if the injected eggs are arrested in development such that they are still eggs after the incubation period. This does not appear to be an art-accepted use of the term for eggs

that develop during the incubation period. The specification uses the art accepted term "embryo" to refer to the egg following 24 hours of incubation (paragraph [0024]). Claims 4-13 depend from claim 3.

Claim 10 is further unclear by use of the terminology "promoter for golden zebrafish". It is unclear if it is referring to a promoter designed for use in golden zebrafish, is a promoter that works only in golden zebrafish or is a promoter isolated from golden zebrafish. Claim 11 depends from claim 10.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Chou *et al.* [Transgenic Research, 10:303-315, August 2001, IDS] or Hsiao et al [**Developmental Dynamics**, 22:323-336, April 2001] as evidenced by http://www.rzpd.de/info/vectors/pCS2plus.shtml (printout attached).

Claim 1 is drawn to a gene fragment comprising a zebrafish α-actin gene promoter, a fluorescence gene (gene encoding a fluorescent protein), inverted terminal repeats from AAV and a basic part from pUC. Claim 2 is drawn to specific plasmid p-αEGFPITR (8.1kb).

Both Chou *et al.* (Figure 1d) and Hsiao *et al.* (Figure 1) taught a plasmid construct comprising the zebrafish α-actin gene promoter operably linked to the EGFP gene encoding a

green fluorescent protein. The expression fragment is flanked by AAV ITRs. Chou taught using the ITR elements in the expression vector as they were known to significantly increase expression in Xenopus embryos (page 304, col. 1, paragraph 2). The vector of Chou *et al.* and Hsiao *et al.* was made by inserting EGFP and the α-actin promoter into a CS2ITR vector. The CS2 plasmid vector has a pUC origin of replication and is a pUC-based plasmid (see http://www.rzpd.de/info/vectors/pCS2plus.shtml, printout attached, which fulfills the limitation requiring a basic part from pUC.

It is noted that pα-actin-EGFP-ITR (8.1 kb) of Hsiao et al. (see page 333, col. 2, paragraph 1) and Chou *et al.* (Figure 1(d), absent evidence to the contrary, appears to be the same as pαEGFPITR (8.1 kb) of claim 2. Evidence that pα-actin-EGFP-ITR (8.1 kb) of Hsiao *et al.* and of Chou *et al.* is not the claimed pαEGFPITR (8.1 kb) may be sufficient to overcome the rejection as it relates to claim 2.

Therefore, both Chou *et al.* and Hsiao *et al.* meet the limitations of claims 1 and 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 3,4 and 6,7 and 9 remain rejected, rejoined and newly considered claims 1 and 2, and newly added claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Hsiao et al. [Developmental Dynamics, 220:323-336, April 2001] in view of Carvan et al [Ann. N.Y. Acad. Sci. 919:133-147, 2000]. The rejection is maintained and applied to claims 1,2,10 and 11 for reasons of record set forth at pages 9-11 of the office action dated 03/03/2006.

The rejection of claim 3 applies to newly considered and newly added claims 1,2,10 and 11, claims 10 and 11 of which are drawn to the same method as claim 3, differing only in scope with respect to the fluorescent gene claimed and the presence of a pUC backbone. Claims 1 and 2 are drawn to the nucleic acid constructs used in the methods of claims 3 and 4. Claim 10 is limited to a green fluorescent protein gene and claim 11 is limited to EGFP. Hsiao et al. taught use of EGFP. Furthermore, the vector of Hsiao *et al.* was made by inserting EGFP and the α-actin promoter into a CS2ITR vector (page 333, col.2, paragraph 1). The CS2 plasmid vector has a pUC origin of replication and is a pUC-based plasmid (see http://www.rzpd.de/info/vectors/pCS2plus.shtml, printout attached, which fulfills the limitation requiring a basic part from pUC.

Applicant's arguments have been fully considered and are not persuasive.

Applicant appears to argue together both rejections under 35 USC 103(a). Those arguments set forth at pages 11-13 of the Remarks dated 06/05/06 that are drawn to the use of a red fluorescent protein-encoding transgene and are not relevant to or effective in overcoming the rejection based on the claimed transgenic fish as it expresses green fluorescent protein.

With respect to the rejection of claims 1-4,6,7 and 9, Applicant argues that the art is focused on expression in fish embryos rather than in adult fish. In response, the claims are not limited to adult fish and to the extent that the claims read on embryos, the art makes obvious the

claimed subject matter. Additionally, because Hsiao et al. used what appears to be the same transgene encoding GFP, there is no reason to believe that it would not be visible in adult fish, including leopard, albino and golden strains. These fish are all of the same species, different only in pigment pattern and amount. Thus, visible fluorescence in adult fish would be an inherent feature. Applicant suggests that by teaching fluorescence in embryos rather than in adults, the references teach away from the use of adult fish. In response, none of the cited references suggests that fluorescence cannot be observed in adult fish and there is no evidence that would suggest that the presence of scales, especially in unpigmented fish, would block fluorescence. In fact, Hsiao, at Figure 3, shows 30dpf fish expressing GFP. These fish are beyond larval stages and have scales.

Claims 5 and 8 remain rejected and newly added claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsiao et al. [2001] in view of Carvan et al [2000] as applied to claims 1-4,6,7 and 9 above, and further in view of Finley et al, [Biotechniques, 31:66-72, July 2001]. The rejection is maintained for reasons of record set forth at pages 11-12 of the office action dated 03/03/2006.

The rejection of claim 3 (above) applies to newly added claims 12 and 13, which are drawn to the same method as claim 3, differing only in scope with respect to the fluorescent gene claimed and the presence of a pUC backbone. Claim 12 is limited to a red fluorescent protein gene and claim 13 is limited to dsRed. As set forth in the rejection set forth at pages 11-12 of the office action dated 03/03/2006, Finley taught the red fluorescent protein DsRed. Furthermore, the vector of Hsiao *et al.* was made by inserting EGFP and the β-actin promoter into a CS2ITR

vector (page 332, col.2, paragraph 1). The CS2 plasmid vector has a pUC origin of replication and is a pUC-based plasmid (see http://www.rzpd.de/info/vectors/pCS2plus.shtml, printout attached, which fulfills the limitation requiring a basic part from pUC. To the extent that Finley, in combination with Hsiao and Carvan (above), renders obvious claims 5 and 8, Finley also renders obvious the methods of claims 12 and 13.

Applicant's arguments have been fully considered but are not persuasive.

Applicant also argues that Finley is directed to (i) 3-color imaging in embryos and (ii) expression in mosaic form. Applicant's argument to the rejection as it relates to embryos vs. adult fish is addressed in the rejection immediately above. That Finley observed expression in mosaic form is not relevant to the instant rejection. Finley is only relied upon as teaching an obvious substitute for other visible marker genes, namely GFP. The specific color it produces, the pattern of expression or when it is visualized is not relevant to the use of the teachings in combination with Hsiao and Carvan in arriving at the claimed invention.

Applicant also argues that simple substitution of a red fluorescent protein for EGFP cannot be accomplished with a reasonable level of success (page 12, paragraph 3). In response, it appears that the claimed DsRed construct is merely a substitution of EGFP in the EGFP construct. Therefore, there is no evidence supporting this assertion. However, Applicant continues by arguing that other red fluorescent proteins, those other than DsRed, are not suitable in achieving viable, adult fish. In response, the claims are not limited to adult fish. Furthermore, claim 7 is not limited to DsRed and evidence supporting Applicant's assertion that other red fluorescent proteins would not be successful in generating red fluorescent fish would necessitate a rejection of the claim under enablement. Finally, evidence supporting that DsRed is the only

effective red florescent protein useful in carrying out the claimed invention would not be effective in obviating the instant rejection because DsRed was known and used in transgenic zebrafish prior to the time of filing of the instant application. As set forth above, Hsiao taught the instantly claimed fish using an EGFP marker gene. Finley taught DsRed as an effective marker gene in zebrafish. Without evidence to the contrary, it would have been obvious at the time of filing to replace the EGFP marker gene of Hsiao with the DsRed gene to obtain fluorescence of a different color.

Conclusion

No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632